Pulsatile release from a flat self-oscillating chitosan macrogel

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Abstract

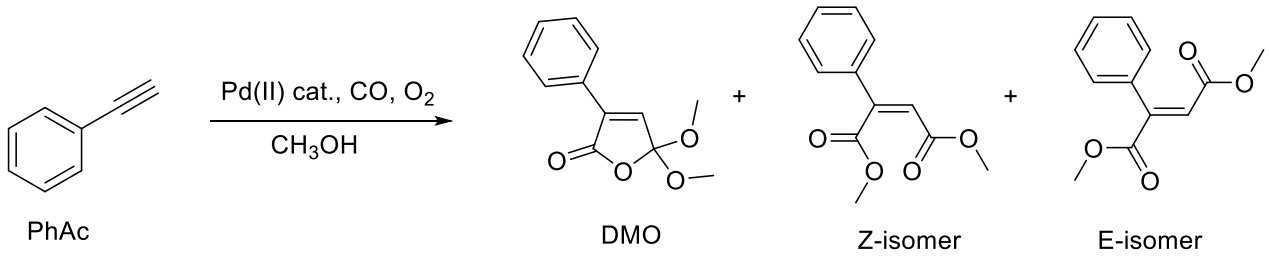
Coupling oscillatory chemical reactions to smart materials which can respond to external stimuli has long been considered an answer to the long-standing issue of pulsatile drug delivery. Although a number of coupled architectures exist, there are no systems reporting pH-controlled pulsed drug release based on chemical oscillators. In this paper, we report for the first time a proof-of-concept self-oscillatory chitosan macrogel, employing the palladium-catalysed oxidative carbonylation reaction as the driving force of its oscillations. The reported hydrogel is composed of highly biocompatible components and a novel imine-functionalised chitosan-palladium catalyst with zero leaching rates. This macrogel was shown to rhythmically release not only the products of the reaction, but also fluorescein, which is used as an FDA-approved model drug. The step-wise release pattern corresponded to the step-wise dynamics of pH decrease in methanol:water, while in pure methanol, the changes in pH had an oscillatory mode, accompanied by mirrored oscillations in fluorescein concentration. This proof-of-concept system significantly expands the horizons of pulsatile delivery materials for future research.

1. Introduction

Pulsatile drug delivery is a cornerstone issue in personalised pharmacotherapy, particularly in chronopharmacotherapy, where drug dosing at specific intervals is shown to give improved outcomes for the patient.[1–3] One possible route towards pulsatile delivery is through the coupling of smart materials, capable of responding to external stimuli, to oscillatory chemical reactions.[4] For example, oscillations in pH or redox properties within one single hydrogel architecture can serve as a stimulus, inducing swelling and collapsing of that hydrogel and resulting in the pulsed release of a drug load. Despite the existence of several smart material/chemical oscillator model systems, fabricated by Yoshida *et al*,[5–7] or membrane/oscillator diffusion systems, fabricated by Siegel *et al*,[8–10] oscillation-controlled pulsed drug release has not been reported before. While the reported self-oscillating systems

represent ground-breaking developments, they are short lived in batch mode and operate only on a micro-scale.[5] To fully materialise the chemical oscillator–smart material actuator concept, an oscillatory chemical system capable of operating under batch conditions for long periods of time is needed.

The palladium-catalysed oxidative carbonylation (PCOC) reaction is a strong candidate for use as a driving force for the oscillations within the smart hydrogels..[11-13] PCOC has a number of advantages: (a) some of the reagents it uses are present naturally in the human body in amounts potentially sufficient for the reaction to proceed, i.e. methanol (MeOH) is produced endogenously in concentrations of 0.5-2 mg/L[14], or its analogue ethanol is also produced endogeneously[4,15,16] and carbon monoxide (CO) is produced naturally by the human body as a signalling molecule at a rate of 0.42 mL/h in a healthy man;[15,17] (b) it operates in a batch-like mode, yielding pH oscillations over several weeks, making in-vivo applications plausible[18]; (c) it has an impressive substrate and catalyst versatility, which can be used to build all-polymeric systems[19–21] and (d) when phenylacetylene (PhAc) is used as a substrate, the reaction produces a number of well-studied products that can be separated and quantified by GC-MS (Scheme 1), making this system straightforward to study under laboratory conditions, and allowing for predictions to be made for the PCOC system employing polymeric substrates in place of small molecule phenylacetylene.[22]



Scheme 1. General scheme of PCOC using phenylacetylene (PhAc) as a starting material.

The work presented here offers crucial findings. Firstly, an imine-functionalised palladium-bearing chitosan polymer, Chi-IM-$PdCl_2$, is shown to be a viable catalyst in the PCOC system. This is only the second polymeric catalyst shown to yield pH oscillation in PCOC systems, the first one being polymer-bound FibreCat® (di(acetato)dicyclohexylphenylphosphinepalladium(II))[21]. Employing Chi-IM-$PdCl_2$

polymer, chitosan and the crosslinking agent genipin, macrogels were synthesised and also shown to be viable in the oscillatory PCOC reaction. Chitosan was selected as a backbone for the polymeric Pd-catalyst (Chi-IM-$PdCl_2$), as well as a core constituent of the macrogels due to its biocompatibility, biodegradability, bioadhesivity, bacteriostatic effects, osteoinductivity, and potential for medical applications.[23–27] Macrogels were studied in two environments, neat MeOH and a MeOH:H_2O mixture (1:1) and in both cases desirable non-linear dynamics in pH, substrate consumption and product formation were captured. Most importantly, the macrogels loaded with a model drug molecule (fluorescein) demonstrated a release of fluorescein concomitant with the pH dynamics.

2. Materials and methods

2.1 Materials

Materials were used as received: palladium chloride (≥99.9%), chitosan medium molecular weight, 2-pyridinecarboxaldehyde (99%), sodium chloride (ACS reagent, ≥99.0%), genipin (≥98% (HPLC), hydroiodic acid (≥57%), phenylacetylene (98%), methanol (HPLC Plus, ≥99.9), all Sigma Aldrich); naphthalene (extra pure), potassium iodide (≥99% GPR RECTAPUR®), all VWR Chemicals; buffer solutions: pH 2.00 (glycine), pH 7 (phosphate) and pH 10 (borate) (all NIST Standard, ready to use for pH measurement, Fisher Chemical). Pure air and CO were supplied by BOC.

2.2 Chi-IM-$PdCl_2$ synthesis

Chitosan (Chi, 0.5 g) was mixed with 2-pyridinecarboxaldehyde (300 mg) in diethyl ether (50 mL) over water-absorbing particles (40 mesh) for 18 h. The precipitate was separated from the particles, collected by filtration and dried in vacuo overnight. Success of the reaction was confirmed by Fourier-Transform Infrared (FTIR) spectroscopy (see Electronic Supplementary Information (ESI) for details). The resulting Chi-IM polymer (0.622 g) was stirred with Na_2PdCl_4 (250 mg) in MeOH (50 ml) to yield Chi-IM-$PdCl_2$ (0.703 g).) The Pd content was measured by inductively coupled plasma optical emission spectrometry (ICP-OES) as 14.27%.

2.3 Macrogel fabrication

Chi-IM-$PdCl_2$ containing gels were fabricated in a simple procedure as follows: chitosan solution (2 mL, 1% wt in 1% vol acetic acid in water), Chi-IM-$PdCl_2$ catalyst (100 mg), genipin (200 µL, 1% wt solution in water) and fluorescein solution (200 µL, 5% wt in 1% wt sodium hydroxide in water) were all charged into a plastic diamond-shaped weighing boat (dimensions 78 mm × 56 mm × 14 mm), evenly distributed on the bottom and thoroughly mixed together. The weighing boat was closed and pressed with another weighing boat, heated in air (37 °C) for 24 h to give a parallelogram-shaped flat gel of emerald colour with inserts of dense particles of the catalyst. A dummy gel was fabricated using the same procedure without the addition of catalyst.

2.4 PCOC using Chi-IM-$PdCl_2$ as a catalyst

The reaction was performed at approximately 20 °C in a flat-bottom Erlenmeyer flask (100 mL) at constant stirring, using the HEL MicroNOTE system to log pH and temperature within the bulk of the reaction. Prior to the reaction, the pH probe was calibrated at room temperature against NIST-traceable buffer solutions of pH 2, 7 and 10. KI (4.150 g), Chi-IM-$PdCl_2$ catalyst (200 mg) and naphthalene (256 mg), added as internal standard, were all charged into the flask in their solid state and suspended in HPLC grade MeOH (100 mL) by stirring. The pH and temperature monitoring started while the solids were dissolving and continued throughout the experiment. The stabilisation of pH indicated that the dissolution of KI was complete. Then, CO and air purging through the solution at flow rates of 15 mL/min each commenced. After an initial pH drop, the value stabilised, and the phenylacetylene (1.38 mL (12.57 mmol)) was added. The pH and temperature were monitored for 2000 min. Samples of the reaction mixture were taken at the end of the reaction and analysed using GC-MS to determine starting material conversion as well as product content. Products were observed in significant amounts: E-isomer = 6.7 mmol; DMO = 5.4 mmol; Z-isomer = 0.2 mmol. Besides the main products, some other products were observed, too, which are generally perceived as intermediates:[28] methyl atropate (0.14 mmol); phenyl cinnamate (0.025 mmol).

2.5 PCOC using macrogel as a catalyst in methanol only

KI (4.150 g) and naphthalene (128 mg) were dissolved in MeOH (50 mL) in a 100 mL beaker. The macrogel (70 mm x 45 mm) was inserted into the solution and a small stir bar (5 mm) was added at the side. The pH and temperature probes were kept away from the gel. The pH was left to stabilise and then CO/air purging through the solution at 15 mL/min each commenced. After 15 min of purging, phenylacetylene (0.69 mL (6.28 mmol)) was added to the reaction. After the pH stabilised again, 100 µL of dilute HI solution was added (0.0228 mmol) to induce oscillations. The reaction was monitored for 4000 min. Samples (0.4 mL) to determine product release and photoluminescence intensity (PL) were withdrawn at the indicated time points. Substrate (phenylacetylene) consumption and product (DMO, Z-isomer, E-isomer, Scheme 1) formation were measured by a Varian Saturn 2200 Gas chromatography with Mass spectrometry detector (GCMS) fitted with a VF-5ms column (30 m). PL intensity was measured by a FLUOstar® Omega UV-Vis. See ESI for details.

2.6 PCOC using macrogel as a catalyst in methanol:water system

Naphthalene (64 mg) was dissolved in MeOH (25 mL). Following this, DI water (25 mL) was added under continuous mixing. The resulting solution was used to dissolve KI (4.150 g) in a 100 mL beaker. The macrogel (70 mm x 45 mm) was inserted into the solution and a small stir bar (5 mm) was added to the side. The pH and temperature probes were kept away from the gel. pH was left to stabilise and then CO/air purging through the solution at 15 mL/min each commenced. After 15 min of purging, phenylacetylene (0.69 mL (6.28 mmol)) was added to the reaction. After the pH stabilised again, 100 µL of dilute HI solution was added (0.0228 mmol) to shorten the induction time. The reaction was monitored for 4000 min. Samples (0.4 mL) to determine product release (GC-MS, ESI) and PL intensity (FLUOstar® Omega UV-Vis, ESI) were withdrawn at the indicated time points.

3. Results and discussion

At first, a chitosan-based palladium catalyst was synthesised (denoted as Chi-IM-$PdCl_2$), via imine chemistry, and used as prepared in the PCOC reaction, employing PhAc as a substrate, in order to confirm that it generated oscillations (Figure 1).

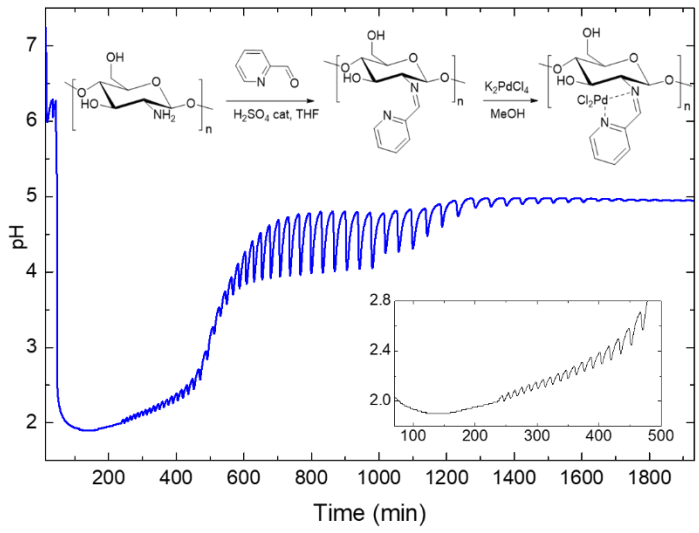


Figure 1. Scheme of synthesis of a chitosan-based palladium catalyst (Chi-IM-$PdCl_2$). Oscillations in pH recorded in the oxidative carbonylation of phenylacetylene in methanol at 20 °C using Chi-IM-$PdCl_2$ as a catalyst. Inset shows the start of oscillations at 244 min.

This is the first time that a chitosan-based catalyst has been shown to yield pH oscillations, indicating the versatility of oscillatory oxidative carbonylation reactions. As can be seen in Figure 1, oscillations in pH had a short induction period of only 244 min and continued for 1600 min until the substrate was almost fully consumed (~93% conversion). Compared to when PdI_2 is employed as catalyst, this is a significantly shorter induction time. On the other hand, the pattern of oscillations looked generally like the pattern observed for PdI_2 systems employing similar conditions.[28,29] The starting amplitude was small and in the region of 0.05 pH units, but developed into 0.8-0.9 pH units with a period ranging from 10 to 40 min.

Chi-IM-$PdCl_2$ was subsequently fabricated into a macrogel (Figure 2A,B), using additional chitosan solution and genipin as a crosslinker rather than more toxic analogues, such as glutaraldehyde, and incorporating fluorescein as a model drug compound.[30] Upon synthesis, these crosslinked macrogels (denoted as Chi-IM-$PdCl_2$ macrogels) formed a thin layer membrane (~0.5-1.5 mm thickness). Since, the Chi-IM-$PdCl_2$ was added into the chitosan solution as a solid (insoluble, crosslinked polymer[31]), the final gel consisted of a chitosan matrix with swollen Chi-IM-$PdCl_2$ particles distributed in it. Scanning electron microscopy images of the soft vacuum-dried dried dummy macrogel and Pd-containing

macrogel are shown in Figure 2C,D. The dummy macrogel has a smooth surface, since it was made from chitosan and genipin solutions only. The Pd-containing macrogel has an uneven surface, consisting of solid Chi-IM-$PdCl_2$ particles of varying size (100-1000 µm), randomly distributed within the crosslinked chitosan matrix. Drying of the gel indicated a water content of 76% (by measuring the weight difference between an as synthesised and a dried macrogel).

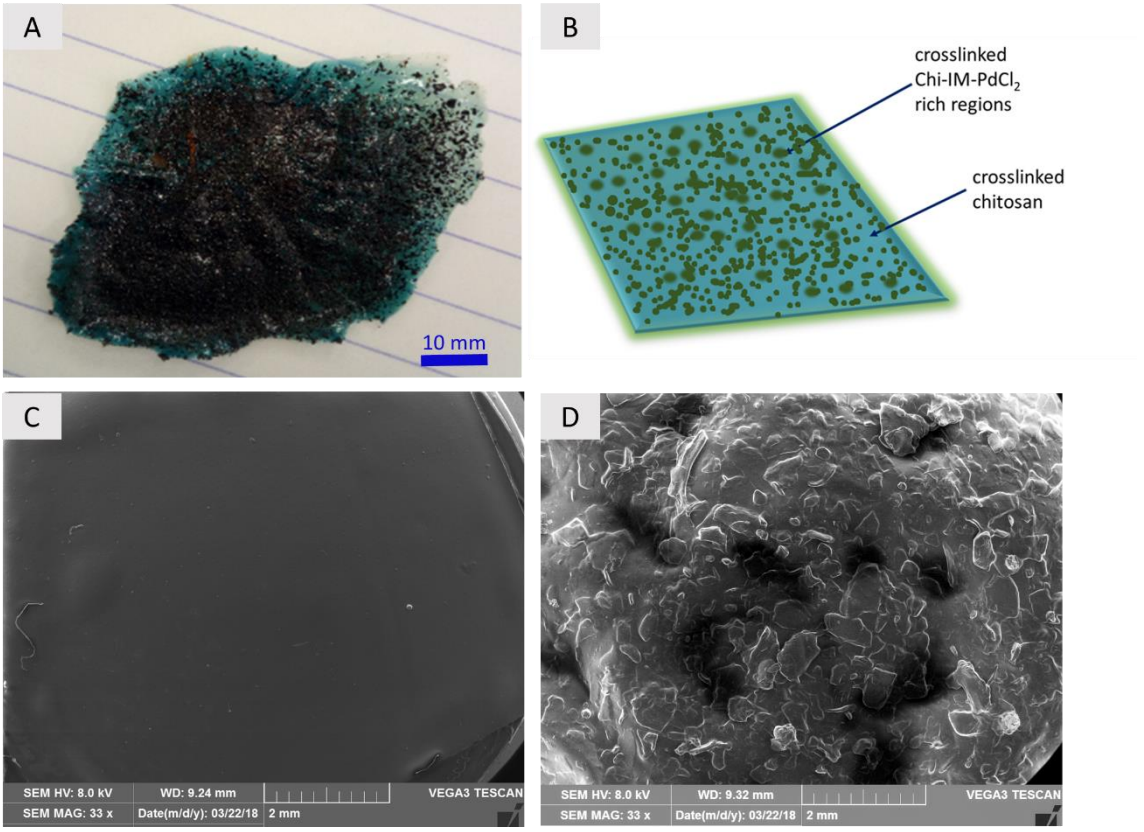


Figure 2. A) Chi-IM-$PdCl_2$ macrogel top view. B) Scheme of distribution of chitosan and Chi-IM-$PdCl_2$-rich regions in the fully cross-linked gel. C) SEM image of a dummy macrogel. D) SEM image of the Chi-IM-$PdCl_2$ macrogel.

Changes in pH in the PCOC reaction system were studied in two different solvent systems – pure MeOH (as in a normal batch-like PCOC reaction) and a MeOH:H_2O system (1:1). Dummy macrogels, comprising of chitosan and genipin but no catalyst, were used for comparison. The reaction was initiated by addition of HI, which helped to induce oscillations, as was observed in our previous study.[21] As can be seen in Figure 3, recurrent non-linear trends in the time series were observed in both solvent systems, however, they had different patterns and significantly different pH ranges. In MeOH, the macrogel gave

typical pH oscillations, demonstrated previously for the similar system employing PdAc or PdI_2 as a catalyst.[21,28] The main difference between our macrogel-catalytic system and previously reported PdAc/PdI_2-catalysed systems is that in the latter, the pH of the reaction media dropped significantly after the substrate was added (for example, from approximately 7 to 3.5 in the PdI_2 system or from 6 to 3.8 in PdAc system), indicating the first conversion stage, with oscillations starting after the pH drop. The same trend in pH behaviour was observed in the Chi-IM-$PdCl_2$ catalysed PCOC reaction (Figure 1). On the other hand, in our macrogel system, no significant drop of pH was observed upon addition of substrate, indicating that at first the substrate was diffusing into the gel, where the catalysis was happening. Indeed, oscillations in MeOH started almost immediately at higher pH values and were sustained over the whole course of the reaction, with a period ranging from 30 to 60 min and a much smaller amplitude (0.1-0.2 pH units) than typically observed in PdI_2 and PdAc systems. While pH in MeOH does not correlate directly with hydrogen ion concentration, higher pH values still indicate smaller hydrogen ion concentrations and in this case small hydrogen ion amplitudes.[32,33] This result suggests the prevalence of autocatalytic steps at higher pH values. As expected, the dummy macrogel in a MeOH PCOC reaction system did not show any systematic pH changes, only a gradual decrease in pH, associated with slow solvent evaporation (Figure 3). No Pd leakage was detected in the system using ICP-OES of the solution at the beginning and at the end of the runs. After removal of the macrogel, no further starting material conversion was observed.

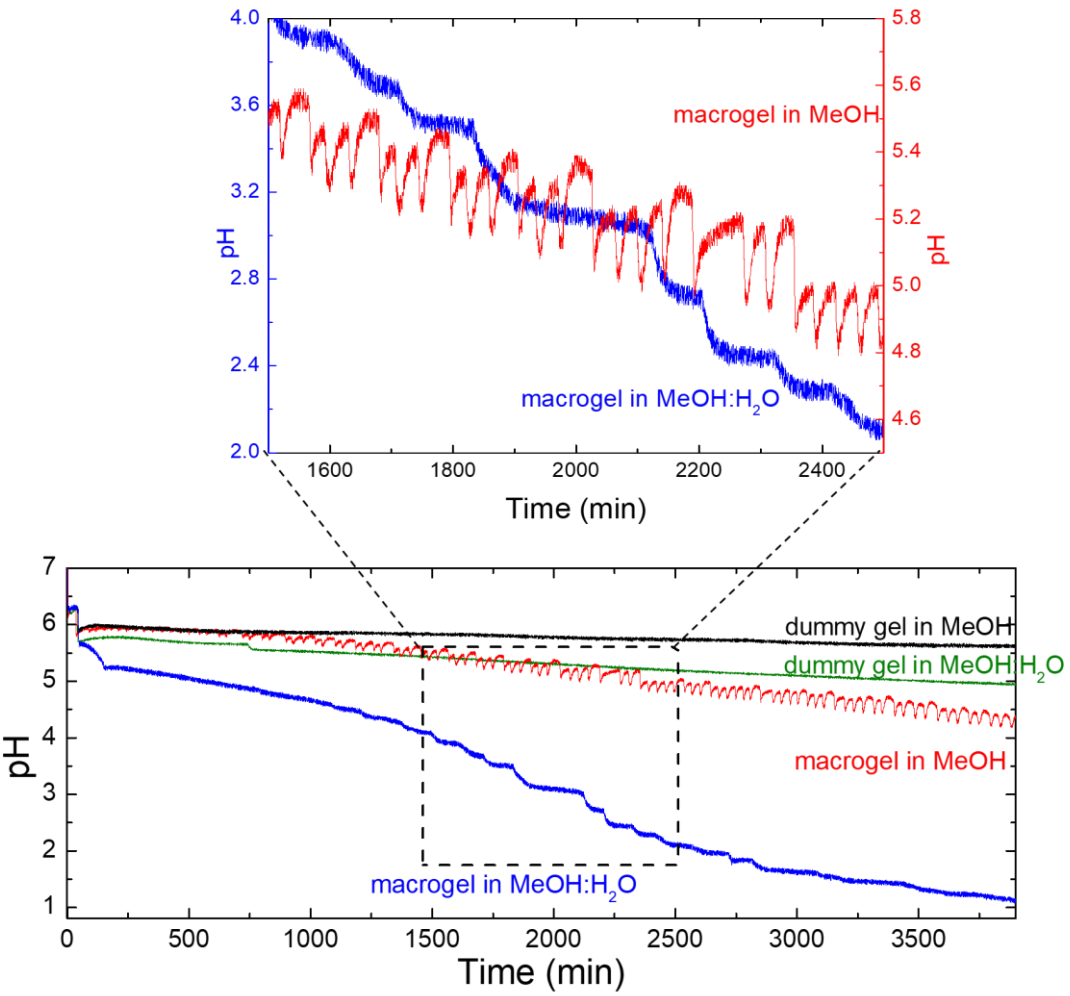


Figure 3. pH trends recorded in the PCOC system employing Chi-IM-$PdCl_2$ macrogels as a catalyst (blue and red data points) as well as chitosan dummy macrogels (green and black data points) as a dummy catalyst and PhAc as a reactant; the solvent systems studied were methanol and methanol:water (1:1). The enlarged region shows pH changes in the PCOC system employing Chi-IM-$PdCl_2$ macrogels as a catalyst in methanol (red) and methanol:water (blue).

In contrast to the pH behaviour observed in neat MeOH, pH decreased stepwise without recovering in the MeOH:H_2O solvent mixture (Figure 3), indicating that the reaction responsible for the pH recovery was either inhibited or concealed by the presence of water. The effect of water on pH oscillations in PCOC was studied previously for the PdI_2-catalysed system – at 20 and 30 vol% water in MeOH, oscillations developed a stepwise character at some point during the oscillatory run. At 40 vol% oscillations were not recorded.[16] This behaviour can be associated with two important factors: (i) the

low miscibility of PhAc with water and (ii) the effect of the addition of water on the formation and consumption of I_2. In the presence of water, following the formation of I_2 (Reaction 1) which subsequently reacts to produce K_2PdI_4 (Reaction 2), the competing Reaction 3 takes place:

$$2HI + 0.5O_2 \rightarrow I_2 + H_2O \quad (1)$$

$$I_2 + Pd^0 + 2KI \rightarrow K_2PdI_4 \quad (2)$$

$$I_2 + H_2O \rightarrow HOI + HI \quad (3)$$

$$5HOI \rightarrow HIO_3 + 2I_2 + 2H_2O \quad (4)$$

According to the mechanism generally accepted for PCOC,[34] Reaction 2 is responsible for regeneration (oxidation) of the catalyst which is reduced from Pd^{2+} to Pd^0 during the conversion of substrate to products. Conversion of substrate is accompanied by the formation of HI and therefore a drop in pH. Reactions 3 and 4 tend to be significant in the presence of metal catalysts,[35] further favouring a drop in pH and dominating over Reaction 2. As Reactions 2 and 3 are competing, an increased amount of water will favour Reaction 3, resulting in a further pH drop. Faster consumption of I_2 by Reaction 3 can limit the amount of I_2 available for regeneration of the catalyst (Reaction 2). Furthermore, the immiscibility of PhAc with water reduces the concentration of PhAc available to react and reduces the reaction rate in the MeOH:H_2O. Both of these factors, the reduced rate of catalyst regeneration and the reduced availability of substrate, would result in the reduced rate of product formation.

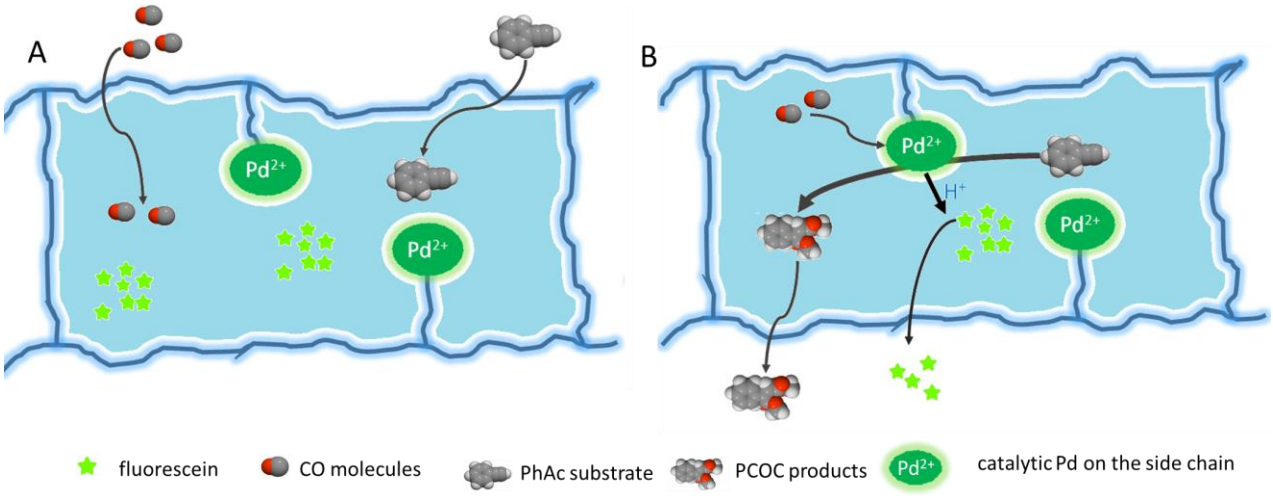


Figure 4. Schematic representation of (A) The diffusion stage of the PCOC reaction in the macrogels. (B) The conversion and release stage of the PCOC reaction in the macrogels.

Since the catalytic system in this work was heterogeneous and incorporated within the macrogel, diffusion of the substrate to the gel surface and/or into the gel was needed for reaction to take place (Schematically represented in Figure 4A). Similarly, the release of reaction products occurred in the opposite direction (Figure 4B).

Figure 5 shows the evolution of starting material conversion (Figure 5A and 5B) and pulsed increase of of Z-isomer product concentration (Figure 5C and D), with the release manner of the other products (E-isomer and DMO) being very similar to pulsed release of Z-isomer (see ESI for details). In both solvent systems, the macrogel exhibited a pulsed release of products, independent of whether the pH oscillated or decreased stepwise. This trend is generally anticipated for homogeneous systems as explained in greater detail in a previous modelling study.[16,19,28] The same trend in a macrogel suggests that transfer of products back to the bulk reaction system was not diffusion driven, i.e. it did not go in the direction of concentration decrease. A higher conversion of reactant was recorded in neat MeOH than in the MeOH:H_2O reaction system. As discussed above, the presence of water was anticipated to reduce reaction rate due to (a) reduced availability of I_2 considered vital for catalyst regeneration and (b) the immiscibility of PhAc with water. The product distribution also differed (see ESI for details). In MeOH, DMO and Z-isomer were the two main products with ~44% and ~48% of total product content, respectively, whereas in MeOH:H_2O, Z-isomer was the main product (~85% of all products formed). In MeOH, product formation was mainly correlated to pH fall within a single oscillation, while in MeOH:H_2O, product formation fully correlated to the pH drop within a single step. Based on these observations, we postulated that in both cases the same process within the overall reaction mechanism was responsible for PhAc conversion to products accompanied by HI formation, as previously explained for the PhAc/PdI_2 oscillatory carbonylation system.[19,28]

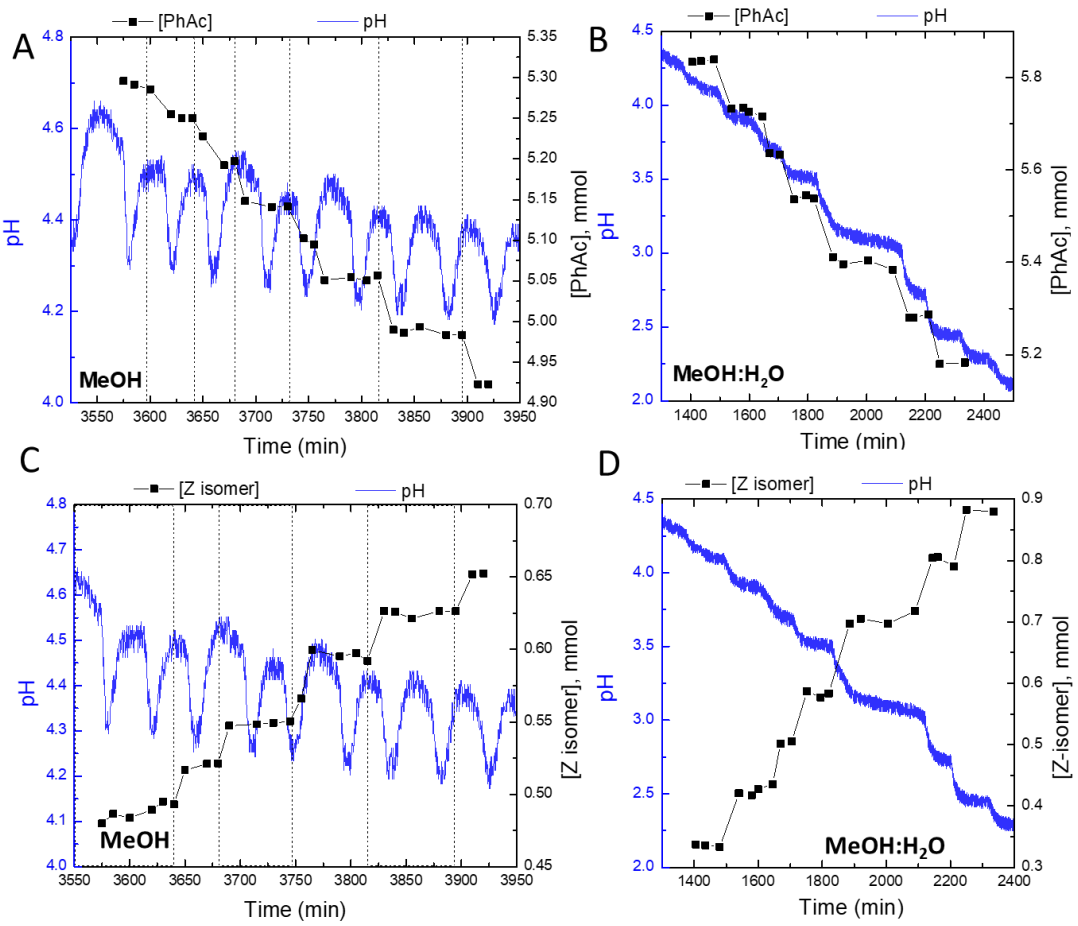


Figure 5. pH-associated pulsed conversion indicated by the concentration of starting material (PhAc) as a function of time in methanol (A) and methanol:water (B). (C) pH-associated pulsed release of Z-isomer as a function of time in methanol. The start of each pulse release in methanol is labelled with dashed vertical lines. (D) pH-associated pulsed release of Z-isomer as a function of time in methanol:water system. PhAc and Z-isomer concentrations are shown with closed symbols, the connecting lines are only as a guide for the eye and do not represent actual data.

pH-controlled release of a drug was studied using fluorescein sodium salt as a photoluminescent tracer incorporated within the macrogel during the fabrication process, with the intensity of photoluminescence (PL) of the reaction solution measured at 530 nm (excitation 480 nm). First, the baseline values were identified in the macrogels while they were stirred in KI solution to make sure that fluorescein was not released without a stimulus. Indeed, the macrogels did not demonstrate any fluorescein release until the addition of HI, used to induce the oscillations.[21] Addition of HI caused a

significant increase in emission intensity in both Pd-containing macrogel solutions and dummy macrogel solutions (Figure 6, closed and open symbols, respectively). In dummy macrogels (no catalyst present), the PL intensity did not change during the reaction, in line with the absence of oscillations or any other significant pH changes. In Pd-containing macrogels in MeOH, the PL intensity kept rising, in line with the oscillations, until the end of the reaction.

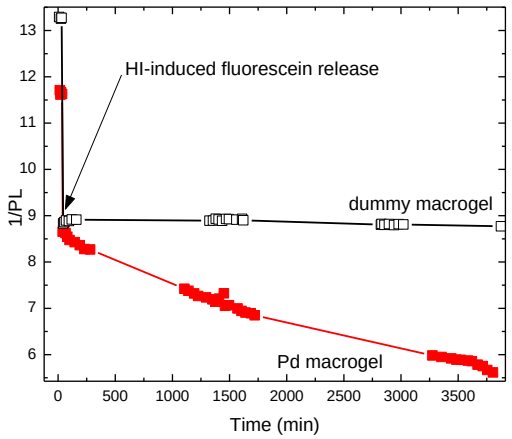
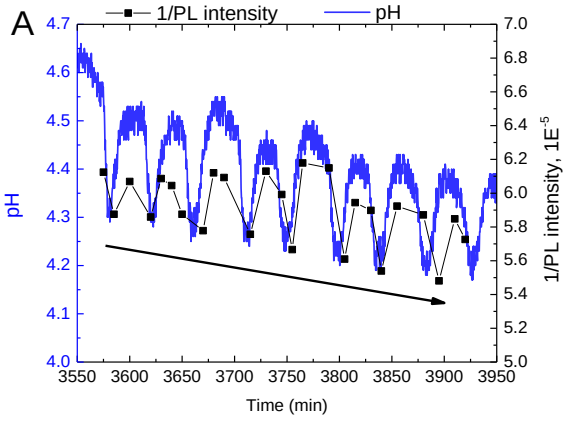


Figure 6. Release of fluorescein from a dummy gel and Chi-IM-$PdCl_2$ macrogel in methanol, expressed as inverse photoluminescence intensity (1/PL). 1/PL is presented as closed symbols in Pd-containing macrogels, and as open symbols for dummy macrogels. The connecting lines are only as a guide for the eye and do not represent data.

A closer look at the character of fluorescein release in MeOH revealed unexpected results (Figure 7A). The release of fluorescein occurred in an oscillatory mode, fully synchronised with oscillations in pH. The maximum PL intensity was observed when pH was low and when the pH increased, the PL from fluorescein decreased. This suggests that fluorescein was released and then reabsorbed by the macrogel, which further suggests that certain changes occur in the gel in response to pH oscillations. While reaction rate governed the substrate conversion to products in a stepwise manner, fluorescein release appeared to be diffusion-governed. The gradual decrease in 1/PL was correlated with a gradual decrease in pH which again indicated a link to changes in macrogel volume and porosity. The general dependency of fluorescein PL on pH also cannot be fully excluded, however, reports have shown that PL intensity increased directly according to pH increase.[36,37] Here, we observed an opposite process. Reabsorption

of fluorescein salt into the macrogel should also not be excluded, since a similar effect has been observed in artificial polymeric membranes.[8,38] Buffering effects have been confirmed to completely damp the oscillations in pH,[38] however, due to the nature of the fluorescein sodium drug, pH oscillations in our case were sustained, but reabsorption occurred in the region of fluorescein pKa (pH 4.4).[39]

The same macrogel in MeOH:H_2O demonstrated a totally different behaviour (Figure 7B). Fluorescein was not reabsorbed but released in steps which correlated with a decrease in pH. This again suggests diffusion controlled fluorescein release, aligned with a stepwise decrease in pH and an anticipated stepwise increase in macrogel volume. A decrease in pH, i.e. increase in hydrogen ion concentration, is known to induce swelling in chitosan based hydrogels due to the protonation of -NH_2 groups resulting in an increase in porosity and therefore increase in load diffusion.[40–43] As results for both MeOH and MeOH:H_2O solvent mixtures indicate rhythmic changes within the macrogel, further experimental studies are planned.



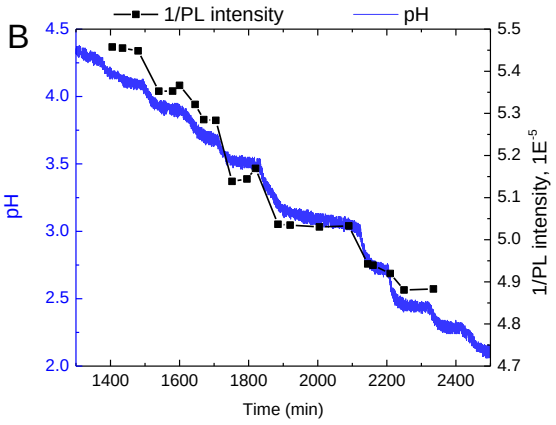


Figure 7. pH-controlled release of fluorescein as a function of time in (A) methanol and (B) in methanol:water systems. Inverse PL intensity is presented as closed symbols. The connecting lines are only as a guide for the eye and do not represent data.

In this study, accurate recording of changes in the macrogel volume were not performed and therefore only observations made with the naked eye are reported. In MeOH, as expected, the Pd-functionalised chitosan macrogel collapsed. Further changes in volume could not be observed by the naked eye. In MeOH:H_2O, the Pd-functionalised chitosan macrogel did not experience volume fraction changes that could be observed by the naked eye. This is associated with the fact that local volume fraction changes in the macrogel would be undetected due to its large size. Further studies are planned in a specially designed optical set-up to assess change of volume in gels in response to changing pH.[44]

4. Conclusions

Using chitosan-based palladium catalyst macrogels, we employed an oscillatory oxidative carbonylation reaction as a driving force to establish a pulsed release of 'drug-like' fluorescein in both neat methanol as well as methanol:water (50:50 vol%) systems. Although the changes in volume of the macrogel were not traced due to the macrogel size, results indicate that volume is changing as a function of pH dictated by the oscillatory chemical reaction. In methanol, fluorescein was released in an oscillatory manner, while in the methanol:water system, release was step-wise. These results fully correlate with pH trends recorded in these systems, indicating diffusion driven release aligned with anticipated changes in macrogel volume as a function of pH. In both solvent systems we confirmed the step-wise conversion of reactant as well as step-wise formation of the reaction products suggesting that the rate of reaction determines this process. Future work will focus on capturing changes in gel volume, exploit the limitations of the system and provide an opportunity to expand it beyond the demonstrated options.

Conflicts of interest

No conflicts of interest to declare.

Acknowledgements

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